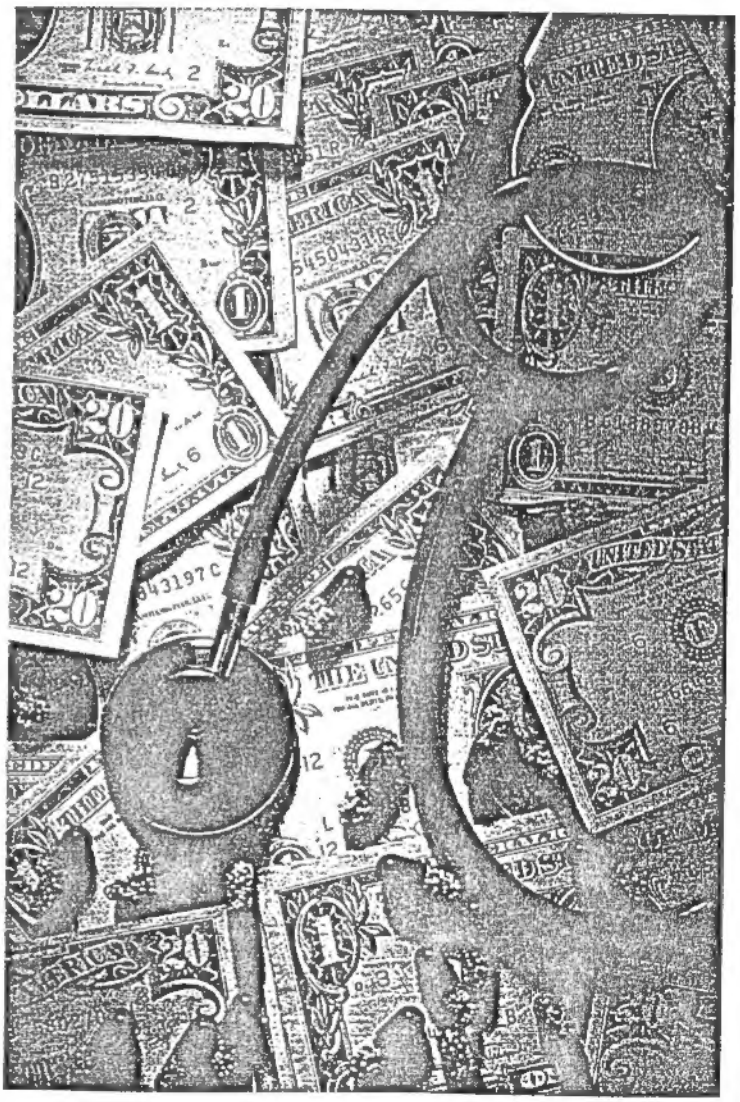
A Primer on Pharmacoeconomics

By Jean Paul Gagnon, PhD

While most other new health care technologies still lack a system for analyzing their value to health care institutions, the pharmaceutical industry introduced the discipline of pharmacoeconomics over eight years ago.[1] The development of pharmaceutical assessment methods has proceeded at a more rapid pace because of several driving forces: (1) the increased sophistication of HMOs and hospitals (e.g., forming their own value analysis groups) and the establishment of a pharmacoeconomic center by the Department of Defense; (2) increased sensitivity to prices; (3) the high-price of biotech drugs as a result of increasing research and development costs; (4) the establishment of pharmacoeconomic guidelines by foreign governments (e.g., Canada and Australia), which has stimulated the use of pharmacoeconomic studies and models; and (5) the use of pharmacoeconomic information by pharmaceutical manufacturers for marketing purposes.



Furthermore, many managed care managers have shifted their focus from demanding information on the intermediate variables of the cost, safety and clinical efficacy of pharmaceuticals to information on the final variables of practice efficacy and the value of the products available from a pharmaceutical manufacturer. Managed care managers believe there is a significant difference between clinical efficacy (i.e., the net benefits of a pharmaceutical product under optimal conditions) and practice efficacy (i.e., the net benefits of a pharmaceutical product under the usual conditions experienced in their institutions). They will no longer settle for information on intermediate variables. They want practice efficacy and safety data, quality of life measurements and value.

> Pharmacoeconomics studies the economics of and value associated with pharmaceuticals.

The objectives of this article are to define the new discipline of pharmacoeconomics; discuss its importance; present a framework on the components of a good study; describe costs, outcomes and the economic tools used in the assessment of pharmaceutical products; review the use of incremental cost analysis; discuss the issues and limitations associated with assessing the value of pharmaceutical products; and consider what might happen in the future.

Pharmacoeconomics

Pharmacoeconomics studies the economics of and value associated with pharmaceuticals. Within this discipline, the costs and outcomes of alternative pharmaceutical therapies are identified, measured and compared. This relatively new discipline addresses choices and focuses on getting the best value at the best price. One of the objectives of pharmacoeconomic analyses is to supply value data about a product. Value data are obtained by merging costs and outcomes in a manner that allows the user to assess the value of the products being compared.

In the discipline of pharmacoeconomics, drugs may be compared with each other or with other modalities, e.g., surgery or devices. The results from pharmacoeconomic studies, models, or analyses are used to build the pharmaceutical formularies that managed care organizations use to manage their pharmaceutical costs. The value of pharmacoeconomics has expanded exponentially as managed care organizations use analyses to make management decisions about their formularies and reduce costs under capitated systems.

In response to the demand for evaluative data, pharmaceutical companies have been quick to develop information that can be used to show the value of their products. The importance the pharmaceutical industry places on producing value data for their customers is reflected in the average number of value-type studies and the proportion of clinical studies performed by each pharmaceutical company. As seen in Figure 1, the average number of studies per company in 1988 was 1.7; in 1994 it is estimated to have been 23.7.

The data in Figure 2 show that the proportion of clinical studies that included health economics variables was 2.6 percent in 1988; in 1994 it is estimated to have been 28 percent. As suggested by these data, the industry is investing a significant amount of resources in determining the value of its products.

Figure 1. Average Number of Pharmacoeconomic Studies Per Company[2]

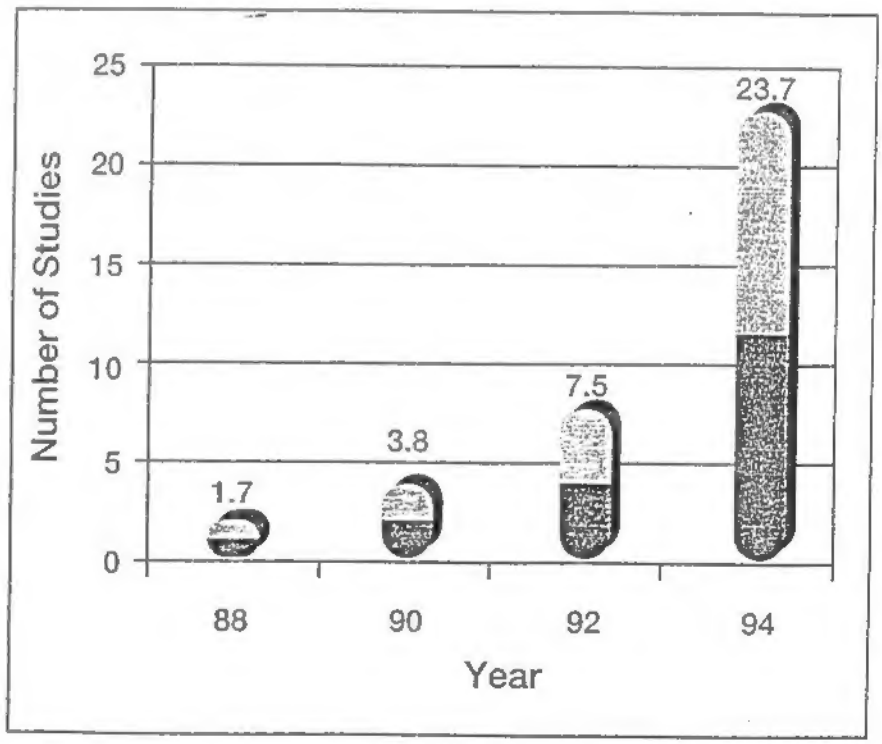
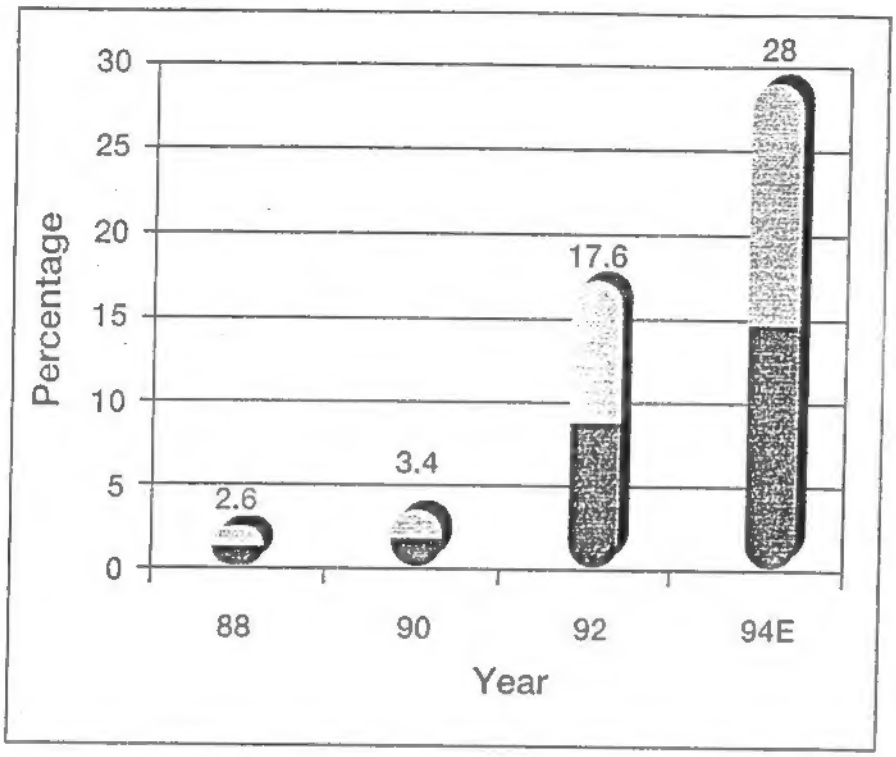


Figure 2. Proportion of Clinical Studies Including Health Economics[2]



Pharmacoeconomics, as a discipline, uses methods and techniques to contrast and compare costs and outcomes to determine a product's value. To determine the value of a product or service, the incurred costs and the achieved outcomes from using the product or service must be identified and compared with those obtained if other options were chosen. The information generated by this discipline is used by pharmaceutical companies to determine prices, plan product development, negotiate pricing with governments and other buyers, justify an indication for use of their product, establish the value of a therapy, differentiate their products from those of other manufacturers and influence public policy.

Framing the Problem

There are a number of steps in performing a pharmacoeconomic analysis. First, the perspective of the study needs to be clearly stated, i.e., whether it is that of the payer, society, community, patient or provider. The best approach may be to use a community perspective (i.e., all of the patients in the catchment area of an HMO or a hospital) because, even if a patient is not a client, the possibility exists that the institution may ultimately be responsible for that patient. Drummond et al[3] emphasizes this type of community perspective. It is also possible that there is more than one audience that should be considered. Second, the question to be addressed in the analysis must be clearly defined. The demographic characteristics of the patients and treatment outcomes to be studied should be included in the question.

> The two major issues of concern within the discipline are the soundness of the research and the interpretation of study results.[7]

Once the decision to do a study or build a model is made and the question has been identified, the user must develop a methodology. A good beginning is to describe the conceptual and practical reasons for choosing the comparators, patients and indications to be studied, and then construct treatment paths to identify all cost and outcome factors to be measured. The tool (e.g., cost effectiveness, cost utility, cost benefit or cost minimization) and the method of data analysis and capture (e.g., prospective, retrospective, randomized, meta-analysis or observational) must be stated. The types of evaluations that will be performed to collect data must be selected. These include economic clinical trials, economic studies piggy-backed onto clinical trials, models using the literature and expert opinion and hybrid approaches that combine trial data with models. If costs are to be incurred and outcomes achieved for more than one year, the values of these factors will need to be discounted using net present value techniques.[4] A sensitivity analysis will also need to be conducted to control for uncertainties and biases. The last step will be to determine how the results of the study or analysis will be communicated to users.

Because the discipline is so new, the tools and nomenclature are still evolving. The discipline now has a journal, *Pharmacoeconomics*, which serves as a forum in which the studies and philosophies of the researchers in the field can be presented. *PharmacoResources*, a newsletter covering news and activities occur-

ring within the discipline, is also being published. Nevertheless, the methodologies of pharmacoeconomics are still not standardized, and a large portion of the literature is not terribly good according to Dr. Bryan Luce, Director, Battell Centers for Public Health Research and Evaluation.[5] At least three articles have reported research that supports Luce's observation.[6] The two major issues of concern within the discipline are the soundness of the research and the interpretation of study results.[7] A number of authors, foreign governments, industry associations and at least one university department and one state government group are actively involved in refining guidelines and principles for evaluating the soundness of pharmacoeconomic studies. In interpreting the results, questions related to how to contrast and compare the incremental differences between drugs and how statistical significance applies to economic significance must be answered. In the following sections, the factors to be considered when constructing a sound pharmacoeconomic study and how to interpret the results using incremental analysis are discussed in depth.

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Costs and Outcomes

Costs. Once the need for a pharmacoeconomic study has been determined and the comparators and perspective have been identified, the costs to be used in the analysis to determine a product's value must be identified. Costs can be divided into three groups: direct medical and nonmedical costs, indirect costs and intangible costs.[8] Direct medical and nonmedical costs involve out-of-pocket payments by an institution or organization for drugs, services and products directly needed to fund a procedure (e.g., treat hypertension). Examples of direct medical costs include pharmaceutical costs, physician fees and the cost of diagnostic and laboratory tests. Nonmedical costs include food, transportation, lodging and family care that are incurred as a direct result of the illness.

Indirect costs are costs that occur because of loss of life, absenteeism or loss of work ability from sickness. Examples of indirect costs include those resulting from decreased earning ability and those incurred from having to seek a new type of employment.

Finally, intangible costs are those resulting from pain, suffering, grief and other emotional and psychological effects of sickness and death. Like indirect costs, intangible costs are difficult to measure. Eisenberg notes that intangible costs may be measured by converting them into an accepted unit for measuring outcome such as quality adjusted life years (QALY).[8]

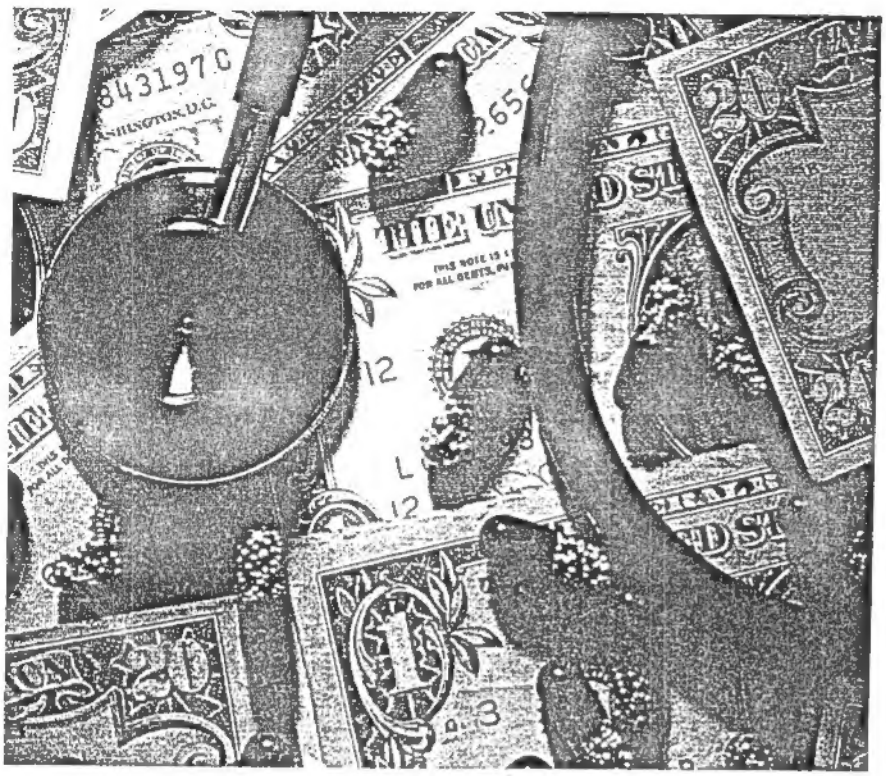
Outcomes. Outcomes measurement is the process of determining what happens to patients as a result of using a product. Many different groups, including health care researchers, payers and providers, are exploring ways to measure health outcomes using scales in questionnaires, surveys and other instruments that measure (1) work and social interactions, (2) psychological well-being, (3) functional capacity and (4) physical ability.

There are many quality-of-life instruments, both disease-specific and general, that are available to measure outcomes. Unfortunately, some instruments have not been adequately tested for reliability and validity. After reviewing many instruments, one group of authors recommends that the selected quality-of-life instrument should focus on global ratings, i.e., patients should be asked to give overall ratings of their quality of life and health-related quality-of-life on a scale from poor to excellent; questionnaires should be used that rate item importance as well as performance; and the instrument should allow patients to supply supplemental written information or comments.[9]

Pharmacoeconomic Models and Tools

There are two classifications of models in pharmacoeconomics: partial and full.[10] Partial models contrast and compare the costs *or* outcomes of drugs with each other or with other modalities. They do not combine costs and outcomes together to determine product value, and they tend to be descriptive (i.e., they present the costs and outcomes data on each comparator). Examples of partial models include outcome descriptions, cost descriptions, cost and outcome descriptions, and cost analysis. One example of a partial model is a consumer reports table. Both outcomes and cost data as well as other decision assistance information are presented, but it is left to the user to determine which product to choose. Another name for this type of approach is *cost consequence analysis*.[11]

Full models also contrast and compare two or more comparators, but they combine cost and outcome to determine a product's value. Examples of full models (in order of



usefulness from low to high) include cost identification or minimization, cost effectiveness, cost utility and cost benefit. Cost minimization or identification involves the comparison of the costs or outcomes of two or more comparators when the outcomes or costs have been found to be similar. In this type of analysis, the treatments have been found through research studies to be equally efficacious; thus, only treatment costs are compared. The objective of this type of analysis is to identify the most efficient comparator.

Cost effectiveness is used to determine which treatment accomplishes a given objective at the lowest cost. This type of analysis uses nonmonetary natural unit outcome measurements (e.g., efficacy percentage for a pharmaceutical product), minimizes program costs, and can only be used to contrast and compare products used for the same indication. Adequate data resources are crucial for conducting an accurate cost-effectiveness analysis. Because of its objectivity, cost-effectiveness analysis is the most frequently used tool in pharmacoeconomics to contrast and compare pharmaceuticals. Cost-effectiveness models used in the analysis of pharmaceutical products are becoming more sophisticated and comprehensive, e.g., some of them include indirect costs and other benefits.[12]

When conducting a cost-effectiveness analysis, the user must supply information concerning: (1) the chosen measures of effectiveness, (2) the source for effectiveness data, (3) the costs that are to be measured, and (4) the source used to determine the costs. The one disadvantage of cost-effectiveness analysis is that it cannot be used to choose among drugs that are administered for different indications, e.g., contrasting and comparing drugs for treating epilepsy with those for treating hypertension.

Another tool used in pharmacoeconomics is *cost utility analysis*. Cost utility analysis differs from cost-effectiveness analysis in that a product's outcome is measured using a quality-of-life or willingness-to-pay measure instead of a natural unit, such as the efficacy value obtained from a clinical study. Otherwise, cost utility and cost-effectiveness analyses are similar with regard to their advantages and disadvantages.

The last measurement tool in pharmacoeconomics is *cost benefit analysis*. In cost benefit analysis, costs and consequences are both measured in dollars. Like cost-effectiveness analysis, it is assumed that the user has unlimited resources, i.e., that the choice implied by the results of the decision analysis will be selected even if it is very costly. Unlike the other tools, cost benefit analysis can be used to compare products for different indications. The disadvantages associated with the use of cost benefit analysis are (1) the difficulty of assigning dollar values to comparator outcomes, and (2) the inability to simultaneously compare products with more than one indication.

> In cost benefit analysis, costs and consequences are both measured in dollars.

There is a definite shortage of people trained to conduct value analyses of new technologies, including pharmaceutical products; thus, many recruiters are looking for individuals with this expertise. Hospitals, HMOs and technology industries need medical schools to form graduate programs that teach health care professionals how to conduct value studies of new technologies.

Incremental Analysis

It is useful to focus the analysis of a cost-effectiveness or other full-model tool on the incremental differences between the outcomes and costs of the products being evaluated. This approach, called *incremental analysis*, provides an analysis of the extra units of outcome per extra dollar spent. Incremental analysis represents the additional cost and effect obtained when one option is compared with the next most intensive or most expensive alternative. It differs from marginal differences which represent the additional cost and effectiveness that can be obtained from one additional unit of service, e.g., one extra dose of a drug per day.[8] Incremental analysis is the standard method by which to compare the costs and effects of pharmaceuticals and other health care technologies and services.

> There are limitations to the tools used to determine the value of a product.

One way of presenting an incremental cost-effectiveness analysis is to arrange the product's effectiveness scores used for the same indication in ascending order, with the incremental differences in costs and effects displayed (Table 1).

Dominance and extended dominance theory[13] is then used to eliminate products not on the frontier of the analysis by comparing a pharmaceutical product with the next more efficacious or costly drug. Using dominance and extended dominance theory, the products on the frontier and inside the envelope can be plotted. (See Figure 3.) In a more sophisticated version, the range of the confidence levels around each effect score can also be included on the chart.

In dominance theory, drugs that are more costly and less effective than alternative drugs are eliminated from consideration. Milton Weinstein suggests[14] that there is a more subtle form of dominance, sometimes called "extended domi-

Table 1. Treatment Regimen Cost Consequence Analysis

Drug	Drug Strength (mg)	Total Therapy Cost ($)	Effect (%)	Change in Cost ($)	Change in Effect (%)	Change in E/C	Date Drug Intro.	Dosage Forms Avail.	Drug/ Drug Inter.	Freq. of Adm.
Placebo	0	0.00	21.8	0.0	21.8	0.00	-	T	1 A	1 BID
E	130	64.08	29.4	64.08	7.6	D	1971	T,IV,IM	4 A	1 TID
F	50	34.02	30.0	(30.06)	0.6	D	1982	C,IV	1 A	1 QID
G	50	15.69	33.6	(18.33)	3.6	D	1984	C,IV,IM	4 A	1 QD
H	50	9.21	48.8	(6.48)	15.2	D	1987	T,L,IV,IM	1 A	1 TID
C	20	119.88	59.2	110.67	10.4	D	1993	T,IV	3 A	1 BID
A	20	26.08	63.3	(93.8)	4.1	D	1985	T,IV,L,IM	4 A	1 QD
B	20	7.29	64.7	(18.79)	1.4	5.893	1978	T,IV	4 A	1 BID
I	30	30.09	70.6	228	5.9	0.257	1983	C	4 A	1 QD
D	10	141.75	84.8	111.66	14.2	0.127	1994	C	4 A	1 QD

D = Dominated, ED = Extended Dominance

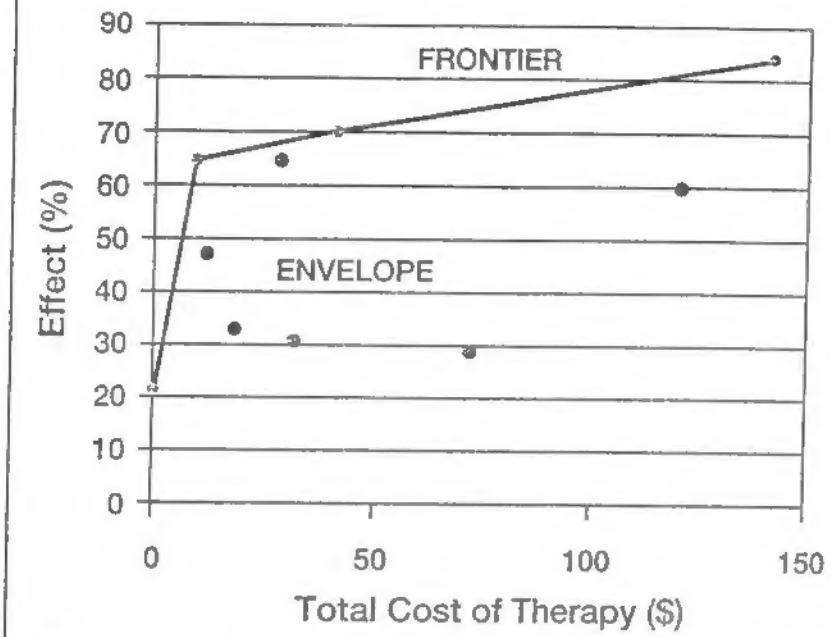
Time to Onset	Comments
0 hours	—
12 hours	Manufacturer had three recalls in last six months
8 hours	Manufacturer can't fulfill regular orders
12 hours	Capsule too big
6 hours	Liquid has aftertaste
14 hours	Pain with extravasation
18 hours	Needs refrigeration
8 hours	Start reconstitution necessary
12 hours	Not compatible with other drugs
6 hours	Not generically available

Dosage Form
T = Tablet
IV = Intravenous
IM Intramuscular
C = Capsule
L = Liquid

Drug/Drug Interaction
1 = no interaction
5 = extreme interaction

Frequency of Administration
BID = twice a day
TID = three times a day
QID= four times a day
QD = once a day

Figure 3. Cost vs. Effect Graph



The frontier is the plotted line and the envelope is the area under the curve.

nance," which arises when the incremental cost-effectiveness ratio for a pharmaceutical product, for example, is less than that for a less costly alternative. In this case the more costly strategy would be selected because the cost per increment is less. Cantor notes "the justification for extended dominance is based on the rationalization that if one is willing to pay a certain amount to gain an incremental benefit, then one would certainly be willing to pay a smaller amount to gain the same benefit."[13] He further states that it is important to notice the presence of extended dominance, because without appropriate adjustments to the results, misleading statements and invalid conclusions can occur. This may result in inadequate allocation of scarce resources. According to Cantor, if extended dominance does exist and budget constraints suggest a mixed strategy for prescribing pharmaceuticals, then ethics dictate that the proportion of the population that receives the less effective treatment be minimized as much as possible.

Modified Cost Consequence Analysis

One approach to assist a user in determining the value for money spent on a pharmaceutical product would be to use a cost consequence *(Consumer Reports)* type of format that included the results from a dominance analysis as well as other key information needed by a decision maker. The effect score could be obtained from the literature using meta analysis and weighted with safety data. An example of such a chart can be found in Table 1. This chart contains the results of the dominance and extended dominance analysis as well as the dates on which the drugs were approved, an evaluation of drug-to-drug interactions, dosage given, time to onset, comments and other information. An investigator would review the information and use it together with his or her knowledge of the institution and its physicians, patients and budget to select a set of drugs for a specific indication. The user would decide which of the drugs would be worth the incremental differences and whether his or her institution can afford to pay the additional amount for the incremental increase in effectiveness. Computer software models that can conduct dominance and extended dominance analyses and build a sophisticated consumer reports type of chart that will allow the user to conduct sensitivity analysis can be developed to make the process more user friendly.

Limitations

There are limitations to the tools used to determine the value of a product. First, these tools may fail to deal appropriately with the values, biases or political perspectives of a particular institution. Second, by selectively choosing costs, an analyst can prove anything. It is also possible that the costs used in the analysis may be irrational and unmeasurable. Third, many of the costs reduced by adding a new product may be overhead costs (e.g., nursing time), which managed care pharmacists say are not under their control. Lastly, measuring the outcome of a new technology can be difficult and subjective. However, instruments are currently being developed that, if proven to be valid and reliable, will allow a more objective measure of outcomes.

Researchers in pharmacoeconomics agree on the economic definitions, importance of perspective, use of incremental costing and discounting, and importance of sensitivity analyses. The major areas of controversy in pharmacoeconomics are focused around indirect cost valuation of added life gains, discount rate, interpretation of economic differences, and range of values for sensitivity analysis.[15] There is still much work to be done before pharmacoeconomics emerges as a true science.

Future

Future analyses of new technologies surely will incorporate the use of tools that evaluate the value of a product in relation to the money spent for it. Products that are shown not to provide value compared with other products will not be allowed on formularies or used in health care systems. Without demonstrated value, a drug or any other technology will only survive by charging a lower price. The days when a company can charge a premium price for a drug that provides only a marginal improvement and then use marketing to drive the product through the distribution channel are numbered.

At the present time, the pharmaceutical industry is being asked to conduct value studies on its products. Customers are asking the industry to conduct these studies for three reasons: (1) they do not have the funds to do this type of research; (2) they do not have the time or expertise to do this type of research; or (3) they do not have the funds to purchase the product so they stall for more time by asking for more sophisticated, time-consuming data analyses.

Few industries in the U.S. are asked by their customers to conduct value analyses of their products and services. This anomaly may change because pharmaceutical companies are finding that, when they present the results of their expensive value studies to customers, customers tend to be suspicious because the study is funded by the company, which may suggest to consumers a potential for bias.[16]

The editors of the *New England Journal of Medicine* noted in a recent editorial that there needs to be some distance between the investigators who conduct the pharmaceutical analyses and the pharmaceutical industry's dollars.[17] They suggest that, if neither the insurance industry nor federal agencies are willing to fund pharmacoeconomic analyses, an independent entity funded by a consortium of companies in the drug and device industry could be created to support economic analyses. Grants from the consortium could support cost-effectiveness analyses on a competitive basis, thus eliminating the concern that support from a single company might lead to bias.

It is conceivable that a number of these types of technology assessment groups could form in the future. Their reports could be in a format similar to the modified consumer reports cost-consequence evaluation using incremental analysis that is discussed in this article. These reports could be used by pharmacy directors in making decisions about new pharmaceuticals and other products. A considerable amount of redundancy could be eliminated and costs saved if these reports were available. Pharmaceutical companies could also use these reports to see how their products compare with those of their competitors. They would still conduct internal quality of life and pharmacoeconomic studies to determine as early as possible whether their new drugs would receive favorable reviews by the consortium and from customers. The existence of assessment consortiums would free pharmaceutical companies to focus their time and dwindling research-and-development funds on the important market functions of improving the quality and value of their products, instead of on conducting expensive economic clinical trials. ■

The contents of this article reflect the views of the author and not necessarily those of Marion Merrell Dow.

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SUMMARY OF ISSUES COVERED IN EXISTING GUIDELINES

Issue	Canadian	Australian	Spanish
Perspective Taken	Evaluation of pharmaceuticals from perspective of society and government payors	Evaluation of pharmaceuticals from perspective of society and government payors	Evaluation of technology from perspective of society
Recommended Techniques to be Included in Analysis	CMA; CCA; CEA; CUA; CBA; More than one technique should be used in analysis;	CEA; CUA; CMA; Does not encourage use of CBA; Includes recommendations for each based on therapeutic claim for drug to be studied.	CEA;CUA;CMA are each described; but no specific recommendations given.
Recommended Alternatives to be Compared in Analysis	Should include comparisons to: existing practice; all relative alternatives doing nothing lowest cost therapy	Should compare with most widely used option or standard medical management.	Should compare with all feasible options when number is limited;
Recommended Source of Data Used in Analysis	Clinical trials with adjustments to capture effectiveness rather than efficacy	Clinical trials supplemented with estimates from reliable sources. Meta analysis is acceptable	Clinical trials with adjustments to capture effectiveness rather than efficacy; Meta analysis is recommended when clinical trials are not possible
Direct Costs to be Included in Analysis		Drugs; medical services; hospital services; diagnostic services; community resources such as long term care	Health resources (not explicitly described); Patients' time; substitutes for HC resources (i.e. long term care).

SUMMARY OF ISSUES COVERED IN EXISTING GUIDELINES

Issue	Canadian	Australian	Spanish
Indirect Costs to be Included in Analysis		Does not encourage inclusion of patient productivity; If indirect costs are included than they must be listed separately.	Lack of consensus on inclusion of productivity. Additional health resources used should be included only if related to treatment.
Recommendations on Cost Valuation	"Economic" rather than "Accounting" definition should be used for capital and equipment; Price/Unit should be obtained through govt. manual	Future costs should be valued at current prices; Price/Unit should be obtained through govt. manual	Use accounts of price per producer unit in analysis; If not available, use the market price that would be in place under "perfect competition."
Recommended Time Horizons	Equal to the duration of pts life following treatment decision; Modelled data can supplement primary data collection	Relate back to treatment; no specific recommendation given.	Equal to the duration of pts life following treatment decision. May be shortened if distant effects are small.
Measuring Outcomes		Acceptable to use proxies for final outcomes indicators; Includes check list to ensure clinical study of adequate quality	Study should include different indicators; Indicators must match objectives of analysis. Indicators describing deaths avoided or lives saved should not be used.

SUMMARY OF ISSUES COVERED IN EXISTING GUIDELINES

Issue	Canadian	Australian	Spanish
Recommended Discount Rates for Analysis	Use rate of 5% for both costs and outcomes; also include rate of 0% in analysis	Use rate of 5% fpr both costs and outcomes.	Use rate of 6% for both costs and outcomes
Recommendations for Handling Uncertainty	Uncertainty due to assumptions made during analysis should be handled through sophisticated approaches such as Monte Carlo simulation.	Provide analysis based on existing data; When possible present outcomes as proabilities on decision tree.	Use expected values; Include sensitivity analysis using central and extreme values.
Presentation of Results	Report in disaggregated detail; Present multiple types of analysis; A structured format will be made available.	Report in terms of the effect per unit of outcome; Report marginal costs for each marginal benefit when relevant.	Summarized and Disaggregated results for outcomes and costs; Present an "Index" of efficiency.
Who Should Do Studies	Should be analyzed independently from manufacturer; may follow same approach as clinical studies.	Overseas clinical trials are acceptable; however economic information should be appropriately adapted.	"Health Authorities" not explicity discussed
When Should Studies Be Done	Guide R&D; Making pricing decisions; When new data becomes available.	Introduction of new products; Changing indications; Changing the price on products;	In authorizing use of technology; Setting prices; Public Financing; To determine incentives for use and dissemination

Measuring "Quality of Life"	Not encouraged; If submitted must include 3 types of measures: generic (i.e. SF36); disease specific; and perference (i.e. Health Utilities Index)	Not required; however; encourages submission of available information.	Generic measures such as health profiles or utility indices should be used in studies where repercussions for quality of life is expected.

SUMMARY OF ISSUES COVERED IN EXISTING GUIDELINES FROM SELECTED COUNTRIES AND GOVERNMENTAL AGENCIES

CATEGORY	ITALY	PhRMA	UK
Perspective Taken	Payer's point of view, but could consider insurance perspectives. If no third party, then patient perspective	Specify target populations	Ideally societal, identifying impact on all parts of society
Recommended Techniques in Analysis	CEA, CMA, and CUA. CBA should not be used.	CEA, CUA, CMA, CBA, CA, QoL, CC	CMA, CEA, CUA, CBA
Recommended Alternatives to be Compared	Use of technologically available and clinically relevant alternatives. Drug comparators should be: 1) in use internationally, as well as in Italy, 2) most widely used in that indication at the time of economic evaluation. Also, all different, relevant alternatives available should be considered. Can be pharmacological or nonpharmacological. Use "do nothing" if no alternatives	Choice of comparator should be stated, e.g., drug, surgical, "do nothing"	Conceptual and practical reasons for choosing comparators should be explained
Recommended Source of Data	New Products: 1) Piggyback on clinical trials in Phase III (prospective), 2) evidence of treatment outcomes from scientific literature Established Products: 1) Available scientific evidence, 2) use meta-analysis	1) Clinical trial and other data bases, 2) expert opinion. All data need to be statistically controlled for confounding variable. Quality of data base should be documented.	Use of one, or a combination, of prospective or retrospective randomized clinical trials, meta-analysis, observational data, and modeling

CATEGORY	ITALY	PhRMA	UK
Direct costs to be Included in Analyses	Costs borne by third-party, e.g., drug costs	Categories of costs should be identified and presented separately (direct medical, non-medical and indirect)	All relevant costs should reflect full opportunity costs, including cost of capital and administration and support costs.
Indirect Costs to be Included in Analysis	No indirect costs	Indirect costs included	All relevant costs
Recommendations on Cost Valuation	Use unit prices and costs from surveys	Resources/costs presented in increments, source and methods for deriving costs/charges should be clearly stated and validated	Physical units reported separately, costs should reflect opportunity costs, including cost of capital and administration and support costs, where relevant average cost data acceptable as proxy for long-run marginal costs
Recommended Time Horizons	- -	Time horizons should be stated and should be based on the likely use and effect of the drug	Treatment paths should be identified
Measuring Outcomes	1) Treatment outcomes that are scientifically sound and representative of the benefits obtainable in routine clinical practice, 2) clinically accurate estimates of the number and types of services provided to patients	Consequences being evaluated (benefit ($), effectiveness, Quality of Life, utility, efficacy, safety, morbidity, mortality). Their sources should be clearly stated.	Outcomes measures should be identified and the basis for their selection reported. When CUA is used, proven generic measures of quality of life are preferred.
Recommended Discount Rates for Analysis	Societal rate of time preference should be adopted and should be fixed at 5%. Discounting must be applied to both inputs and outputs.	Costs should be discounted for analyses with time horizons greater than one year.	Two different bases: 1) additional costs and outcomes at the prevailing rate recommended by the Treasury (6% annum), 2) all costs and monetary outcomes.

CATEGORY	ITALY	PhRMA	UK
Recommendations for Handling Uncertainty	Use sensitivity analysis when economic model is deterministic (i.e., when the statistical distribution of the variable in question is unknown).	Uncertainty should be demonstrated by statistical analysis to address random events and sensitivity analysis to cover a range of assumptions.	Sensitivity analyses should be conducted and reported and the sensitivity of results to all uncertainty in the study explored. Use confidence intervals and/or ranges for key parameters.
Presentation of Results	Use "analysis of extremes," e.g., CEA, consider lowest and highest ratios	A final report should be available which describes all assumptions, methods, and data sources.	Comparisons with results from other studies should be handled with care.
Who Should do Studies	- -	- -	- -
When Should Studies be Done	For new and established products	- -	DoH would like to see CEA for new products but sees this as a matter for purchasers, prescribers, and companies. No right time in product life cycle.
Measuring Quality of Life	Only clinically relevant end-points should be considered (survival, incidence of specific events of interest, Quality of Life). Findings using surrogate end-points should be treated with caution.	Consequences being evaluated (benefit ($), effectiveness, Quality of Life, utility, efficacy, safety, morbidity, mortality) and their sources should be clearly stated.	- -

SUMMARY OF ISSUES COVERED IN EXISTING GUIDELINES FROM SELECTED COUNTRIES AND GOVERNMENTAL AGENCIES

CATEGORY	CENTER FOR DISEASE CONTROL (CDC)
Perspective Taken	Societal but additional perspectives may also be studied when relevant, perspectives should be clearly stated
Recommended Techniques to be Included in Analysis	CBA, CEA, CUA, include marginal or incremental analysis in a prevention-effectiveness study, net present value (NPV) be used as the summary measure in a CBA
Recommended Alternatives to be Compared in Analysis	Include baseline comparator, include all reasonable options, including a current practice or a "no-program" option in CEA
Recommended Source of Data Used in Analysis	- -
Direct Costs to be Included in Analysis	Use resource costs; in CEA only use medical and non-medical direct costs in net-cost equation; in CUA only direct costs should be used in net-cost calculation
Indirect Costs to be Included in Analysis	All measurable opportunity costs incurred, cost of illness approach limited to estimating the cost of disease averted
Recommendations on Cost Validation	Use willingness-to-pay method or other comprehensive measure to value health outcomes; in CBA, use human capital approach to estimate productivity losses in CEA
Recommended Time Horizon	Long enough to capture all benefits and costs in the future as a result of the program
Measuring Outcomes	Willingness-to-pay method or another comprehensive measure in CBA. Cost-of-illness approach limited to estimating the cost of disease averted in CEA and CUA. Final health outcomes should be used in CEA.
Recommended Discount Rates for Analysis	Use 5% real discount for economic analysis, no adjustments for inflation in the future should be made. Discount future nonmonetary health outcomes at 5%.
Recommendations for Handling Uncertainty	Sensitivity analysis should always be performed over the plausible range of values for each variable. Use 0% and 8% discount rates.
Presentation of Results	Distributional impacts of study should be explained
Who Should do Studies	- -
When Studies Should be Done	- -
Measuring Quality of Life	- -